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Antimicrobial Peptides: A new weapon to fight infections. Recent advances and future prospects - A Review

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ABSTRACT:

Antimicrobial peptides are important members of the host defense system and are an evolutionarily conserved component of the innate immune response. These have been demonstrated to kill Gram negative and Gram positive bacteria, mycobacteria, viruses, fungi and even transformed or cancerous cells. These peptides also have the ability to enhance immunity by functioning as immunomodulators. These small polypeptides display hydrophobic/cationic properties and adopt an amphipathic structure, which is essential for their antimicrobial actions, enabling intercalation into bacterial cell membranes creating pores and resulting in osmotic lysis. In this comprehensive review we will discuss about the mechanism of action, application in food industry and future of these antimicrobial peptides.

Key words: Antibiotics, peptide, pathogens, plant, bacteria

INTRODUCTIONS

Antibiotic resistance has turn out to be a worldwide public-health dilemma, thus it is of the essence that new antibiotics continue to be developed [1]. Disease causing microorganisms that have become resistant to conventional antibiotics are an increasing public health problem. There is a fact that about 70% of bacteria causing infections in hospitals are resistant to at least one of the commonly used antibiotics [2]. There are also multiresistant bacteria, some of which are dead set against to nearly all approved antibiotics [3].

The escalating number of patients with impaired wound healing and the development of multidrug resistant microorganisms entail the analysis of alternatives in wound care. The antimicrobial activity of naturally occurring host defense peptides and their derivatives could be one substitute to the on hand therapy options for topical treatment of wound contagion [4]. AMPs, with their range in structure and stuff nature, are a new alternative to predictable antibiotics. The likelihood of the growth of pathogen conflict and/or side effects is much minor with AMPs than chemical antibiotics, because AMPs are naturally a part of human antimicrobial security. Therefore, AMPs are well thought-out to be the basic element of novel antibacterial, anti-fungal, and antiviral drugs in the therapy of infectious diseases [5, 6, 7] and parasitic infections [8] and AMP may also be functional in the treatment of cancer [9, 10,11] and HIV infection [12].
Recent attention has been focused mostly on studying anti-HIV peptides and lections, but the inhibition of bacteria and fungi by these macromolecules such as that from the herbaceous, Amaranthus, has long been known. Thionins are peptides frequently found in barley and wheat are noxious to yeasts and gram-negative and gram-positive bacteria. Fabatin, a recently identified peptide from fava beans appears to be structurally allied to Gamma thionins from grains and inhibits E. coli, P. aeruginosa and Enterococcus hirae [13].

Plants and animals bring into being antimicrobial peptides against their pathogens, either expressed constitutively or induced after pathogen get in touch with [14]. Antimicrobial peptides (AMPs) are an evolutionarily conserved constituent of the native immune response, which is the principal security system for the majority of living organisms, and are found among all classes of life ranging from prokaryotes to humans [1].

The foremost antimicrobial peptide from a eukaryotic organism, wheat α-purothionin, was discovered in 1942 by Balls and collaborators. The next peptide in this class was not reported until 30 years later and studies describing the discovery of new antimicrobial peptides from plant tissues have been converted into numerous only in recent years.

AMPs are component of the fundamental defense line of innate immunity and named defensins for the reason that of their function in host defense. Since then, many other peptides with analogous antimicrobial effects have been discovered and characterized by use of genetic and molecular biological research methods [15]. Several AMPs are able to simultaneously attack a range of microorganisms, including Gram-positive and Gram-negative bacteria, fungi, parasites, enveloped viruses and even tumor cells [9]. Evidences also exists indicating action against a wide range of human pathogens [16]. In addition to standard AMPs, other proteins with antimicrobial properties are known. Lysozyme was the foremost protein reported to have antimicrobial activity. In a while, the antimicrobial activity of histones was confirmed. Since then many other antimicrobial proteins have been described, counting granulysin, produced by natural killer cells and CD8 T cells [17] calprotectin bactericidal/permeability increasing protein from

human neutrophils [18], human lactoferrin [19] and histidine-rich glycoprotein [20].

Antimicrobial peptides (AMPs) are cysteine loaded short amino acid sequences common in the seeds of many species [21]. The range of AMPs discovered is so great that it is difficult to catalog them except broadly on the basis of their secondary structure. On the whole, AMPs can be classified into four most important classes: β-sheet, α-helical, loop and extended peptides, with the first two classes being the most widespread in nature [1].

Plant AMPs are grouped into numerous families and many share common features, such as an overall positive charge, the presence of disulfide bonds (which even out the structure) and a means of action targeting outer membrane structures, such as ion channels. In addition to their function in host defense and their appeal as simple models for studying the molecular mechanism of antimicrobial peptide act, AMPs have the potential to fight pathogens, including those showing increased resistance to conventional antimicrobial compounds [21]. Peptide based antimicrobial protection is an evolutionary ancient mechanism, with instant and non-specific effects against most Gram-negative and Gram-positive bacteria, fungi, viruses and eukaryotic parasites [22, 23, 24].

Antimicrobial peptides (AMPs) are generally composed of 12–50 amino acids. These peptides synthesized by microorganisms as well as multicellular organisms from the plant and animal kingdoms, and they are element of innate host defense mechanisms [25]. Moreover, AMP takes part in the interconnection between innate and adaptive immunity [26].

Antimicrobial peptides have been isolated from a wide diversity of organisms, including animals, bacteria, insects and plants [27]. AMPs themselves are regulated by cytokines created by immuno-competent cells [28]. AMPs act professionally against pathogens without any harm to the host. The structural differences between host and target cell membranes have an indispensable role in the selective action of AMPs [29]. Typically, AMPs follow a common outline of action. Sequence, size, degree of structure formation, cationicity, hydrophobicity and amphipathicity are structural parameters that have key roles in the communication of AMPs with target cells [30].

MECHANISM OF ACTION

Antimicrobial peptides are important members of the host defense system, because they have a broad ability to kill microbes. Antimicrobial peptides form an important means of host defense in eukaryotes. Large antimicrobial proteins (>100 Amino Acids), are often lytic, nutrient binding proteins or specifically target the microbial macro-molecules. Antimicrobial peptides act by disrupting the structure or function of cell membranes in microbes. These peptides have been found in the epithelial layers, phagocytes and body fluids of multicellular animals including humans [31].

Several studies give details of the induction of AMP expression. Pro-inflammatory cytokines, certain bacterial strains as well as other exogenous compounds, have been acknowledged as inducers of endogenous AMPs expression [28, 32, 33]. Schlee and colleagues investigated the stimulatory effect of probiotic bacterial strain *Escherichia coli* on hBD-2 expression and recognized the bacterial factor accountable for hBD-2 induction [34]. These investigators bring into being that the stimulatory effect of this bacterial strain on hBD-2 expression *in vitro* is dominantly mediated through the presence of flagellin. Addressing the not fully explained link between psychological stress and increased vulnerability to microbial infections, Aberg *et al.* showed that psychological stress decreases the levels of two key AMPs in the skin via increased endogenous glucocorticoid production [35]. This data put forward that glucocorticoid blockade could normalize cutaneous antimicrobial defense during psychological stress. Recently, Rabiq *et al.* provided a substitute to conventional treatment of acute infectious diseases such as *Shigella* infections [36]. Based on results of animal experiments, Rabiq *et al.*, propose that orally administered sodium butyrate can mediate a therapeutic effect via induction of endogenous AMP expression and secretion in the colon and rectum. Similar findings were observed in a study investigating the effect of the hormonally active form of vitamin D3 on expression of cathelicidin in both normal and cystic fibrosis bronchial epithelial cell lines [37]. Vitamin D stimulated the expression and secretion of endogenous cathelicidin, inducing antimicrobial activity against airway pathogens *Bordetella bronchiseptica* and *Pseudomonas aeruginosa.* Before human trials begin, however, many unanswered questions should be answered to fully explicate the mode of action of exogenously administered agents (such as butyrate or vitamin D) in inducing innate immunity mechanisms.

The elucidation of the manner of action and interaction with microbes will help out the improvement of peptide design with a view to targeting specific harms in agriculture and providing new tools for plant protection. [38]. Recently, the rapid coming out of microbial pathogens that are resistant to currently available antibiotics has triggered considerable attention in the isolation and investigation of the mode of action of antimicrobial proteins (peptides) [39].

Many signal molecules in mammals, including neuron-transmittors, hormones and growth factors are peptides and take action in multiple cellular processes [40]

Several models that particularly deal with the actions of defensins and linear amphipatic cationic peptides suggest formation of channels through and/or disruption of bacterial membranes [41]. Most AMPs kill bacteria by pore formation in lipid membranes, but other mechanisms of action have been described and projected [42]. Defensins and cathelicidins can inactivate bacterial LPS by binding to the endotoxin moieties [43]. Many peptides take steps directly inside the microorganisms by inhibiting intracellular processes. The aggregate channel model features a mechanism of transport through the lipid bilayer without the formation of a stable channel. Some AMP inhibits DNA synthesis, protein synthesis, or both. Histatin an AMP, targets the mitochondria of fungal pathogens. On the other hand, facts indicate that in addition to pathogen killing, AMPs also have an effect on pathogen metabolism. In some cases they can activate the production of virulence factors, such as the hyaluronic acid capsular polysaccharide [44].

Only thionins and defensins were set up to be active against human pathogen Leishmania donovani. at a low micro molar range of concentrations. Thionins are known as the most active peptides tested until now. They distorted ionic and pH gradients across the parasite plasma membrane together with a quick depletion of intracellular ATP without affecting mitochondrial potential. Hence the lethal effect of thionins was mostly connected to permeabilization of the plasma membrane leading to an immediate death of the parasite. The present work is the first confirmation for leishmanicidal activity in plant peptides. Future prospects for their development as new antiparasite agents on human diseases are well thought-out [45]

ANTIMICROBIAL PEPTIDES IN FOODS

Antimicrobial peptides have captured the concentration of researchers in current years because of their efficiency in fighting against pathogens. Antimicrobial peptides are under consideration as novel substitutes for conventional antibiotics [46].

Adding up preservative is an ordinary way of preventing or slowing microbial growth, the major motive of spoilage and poisoning of food products. However, there is a scarcity of competent and safe preservatives as a result of appearance of resistant forms of food pathogens in reply to massive use of preservatives. On the other hand, minimally processed natural foods are enviable for consumers. As naturally originated compounds, AMPs are advantageous options for bring into play as new preservatives. Among AMPs, the bacteriocins group is the favorite [47]. Since many bacteriocins are efficient against Gram-positive bacteria (Listeria monocytogenes), which cause most of the food born illnesses, bacteriocins are in focus of many studies. Nisin, a bacteriocins which is produced by certain strains of Lactococcus lactis, was permitted as a food preservative by the Joint FAO/WHO Expert Committee on Food Additives in 1969. Nisin significantly inhibits activity of many food pathogens in a broad series of products from dairy products to sea foods [48]. Bacteriocins are not just simple preservatives, but usually have important responsibility in quality and flavor of the food product [49].

Use of natural antimicrobials in food industry is not limited to bacteriocins. Because of the long history of milk use, milk bioactive agents are typically secure candidates for use in food industry. Lactoferrin, the natural iron-binding defense protein in milk, has many commercial applications including its usage as a food preservative [50].

Many plants and animals have been manipulated with antimicrobial peptide encoding genes and several pesticides and drugs have been shaped based on these peptides. Such strategies and products may still have a long way to go before being inveterate by regulatory bodies and others need to conquer technical problems before being accepted as applicable ones. In spite of these facts, several cases of triumphant use of antimicrobial peptides in agriculture and food industry indicate a gifted future for widespread application of these peptides [46].

Antimicrobial peptides as proteins, genes encoding AMPs can also be delivered as gene therapy. The most hopeful treatment under investigation in this area is alternative gene therapy using genetically modified bacteria producing therapeutic AMPs *in situ* for targeted killing of precise pathogenic species, a treatment that can be especially suitable in the treatment of dental caries, Crohn disease and other disorders in which disturbances in natural microflora play a role and host microbe balance must be preserved. Currently, in the era of antibiotic resistance, AMPs are desired novel tool with proven efficiency and the potential for long-standing application [51].

CONCLUSION

Development of confrontation to chemotherapeutic agents shown by the microbes appears to be an never-ending process since the time antibiotics were exposed. So every antibiotic has certain life period regarding its effectiveness. Scientists have realized an enormous potential in natural products from medicinal plants to dish up as alternate source of combating infections in human beings which may also be of lower cost and slighter toxicity. In conclusion, according to the outcome of experimental and clinical studies, AMP plays role in various physiological processes, mostly in innate immunity. These processes, however, must be investigated in detail to evaluate the exact function of

all relevant AMPs and to expose the extent to which AMPs influence the etio-pathogenesis of candidate diseases, such as Crohn disease. Knowledge of physical and chemical properties of AMPs underlies the complete understanding of their mechanisms of act. Even though AMP have been known for decades, they still provide research challenges and are potential agents in the fight against infections and other major diseases, mainly for the reason that they are gene encoded and occur naturally in the human body. Advanced expression systems enable large scale production of therapeutically relevant AMPs, which can be potentially used in the treatment of microbial infections. To better appreciate the nature of AMPs it is necessary to evaluate the functional consequences of genetic polymorphisms and mutations in genes encoding human AMPs. These data will allow elucidation of correlations between impaired AMPs expression and diseases. Beyond direct application of specific AMPs as proteins, genes encoding AMPs can also be delivered as gene therapy. The most promising treatment under investigation in this vicinity is alternative gene therapy using genetically modified bacteria producing therapeutic AMPs *in situ* for targeted killing of specific pathogenic species, a conduct that can be especially suitable in the treatment of dental caries, Crohn disease, and other disorders in which disturbances in natural microflora play a role and host microbe balance must be preserved. Currently, in the era of antibiotic resistance, AMP is a preferred novel tool with proven efficiency and the potential for longterm application. Diverse immuno-modulatory behaviors of such host defense peptides are the most fresh characterized property and will offer an additional stimulus to consideration of these molecules as a new class of therapeutic agents. Further work on isolation and characterization of active principles from medicinal plants and their pharmacodynamic study by means of latest techniques would be highly useful to human beings. The spread of antibiotic resistance increases the significance of developing a clinical role for AMPs. Still a lot have to be discovered for the reward of these molecules in clinical applications and prevention measures for their disadvantages including their low *in vivo* stability, high costs of production and the strategies for their discovery and optimization. These futures will be to provide valuable information that could be useful in the identification of antimicrobial peptides and the exploitation of their therapeutic potential.

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